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Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Land, Rm 1061
Rockville, MD 20852

Reason: Docket Number 02D-0324. Guidance for Industry – Drugs, Biologics, and Medical Devices Derived from Bioengineered Plants for Use in Humans and Animals (Draft Guidance)

To Whom It Concerns:

We would like to comment on the above draft GGP's and related comments made by representatives of the FDA at a "public forum" on the draft GGP's in Ames, IA on November 21, 2002.

As a point of reference, Numedloc has been involved with this technology since 1996 when it initiated discussions to create a joint venture between Agricetus (prior to their acquisition by Monsanto) and a to-be-established producer cooperative which would assume total responsibility for developing GMP's and crop production.

Production Framework A manuscript entitled: "Commercial Production Of Transgenic Crops Genetically Engineered To Produce Pharmaceuticals" accepted by BioPharm for publication is also attached. This manuscript, developed in association with the Prairie Rivers of Iowa RC&D examines practical issues associated with production of transgenic agricultural crops. This manuscript includes a cost evaluation for the approaches proposed and finds that effective regulation is both technically feasible and cost effective. It is proposed as an integrated set of fundamental approaches which should be included in FDA's final GGP's covering GLP's and GMP's for this industry.

Dr. Crosby, who coordinated this effort, has worked for a pharmaceutical company in new drug development including the isolation of new pharmaceuticals from agricultural crops. He also served as Senior Scientist on the National Cancer Institute's Diet, Nutrition and Cancer Program, which pioneered the development of technologies and approaches for objectively defining relationships between the foods we eat and diseases we are at risk for.

Land Ownership At the "public forum" in Ames, IA on November 21, an FDA representative indicated that corporate ownership of land used in the production of pharmaceutical crops was the most appropriate choice, and insured control over the production process. We would like to

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suggest alternative approaches, which can provide the desired control without resorting to large-scale corporate land ownership and operation. Alternative approaches can increase the efficiency of land utilization and minimize landowner conflicts. Land utilization efficiency is constrained by the likely need for crop rotation and a likely requirement for buffer strips. In addition, not all land in a tract will be suitable for transgenic crop production (high environmental risk factors, insufficient buffer space, etc.). Finally, corporations must acquire land before they physically need it for pharmaceutical production. The net result is that direct corporate ownership results in the acquisition of far more land that is actually needed.

At the same time, large-scale corporate ownership of land represents a significant change in public policy. The impact is magnified dramatically if similar requirements are established for the production of industrial chemicals in transgenic agricultural crops. Two approaches are proposed.

First, we propose allowing the creation of agricultural real estate investment trusts (agREIT's). AgREIT's would be established as privately or as publicly traded entities which would acquire land in traditional ways (direct acquisition or UPREIT transactions where land is swapped for stock shares). (We note that in states with anti-corporate farming laws, there is precedence for limiting ownership in corporations involved in agricultural production to individuals. That is, ownership by institutions and corporations would be prohibited. In fact, one could make the case for widespread private ownership of shares re-establishes Jeffersonian democracy.)

The second entity would be a "future generation cooperative" where farmland is the product of record. In this case, land could be removed from the cooperative by the owner, once production requirements were met.

In both cases, we believe that there should be a requirement that land leases from either type of an entity by a pharmaceutical company would be for the life of the drug subject to pharmaceutical demand. We do not want to see production of a drug shifted from field to field to field every year. This creates unnecessary environmental risks. Similarly, the land owning entity should not be allowed to cancel a production lease unless they can document unacceptable human and/or environmental safety risks.

Contract Agricultural Production Few pharmaceutical companies today have any core expertise in agricultural production. Requiring companies to develop internal ag production programs to handle crop production, storage and transportation needs represents inefficient utilization of existing resources (knowledge and expertise). At the same time, we recognize that the production of transgenic crops genetically engineered to produce pharmaceuticals requires special expertise and knowledge far beyond that possessed by traditional farmers. We believe that pharmaceutical companies should be allowed to contract with agricultural production companies whose sole business is to grow transgenic crops genetically engineered to produce pharmaceuticals. These contract producers should be required to meet the same performance criteria as a pharmaceutical company would be expected to meet; and pharmaceutical companies could not abrogate any legal or regulatory responsibility relative to production.

Secure Production Environment Until Human And Environmental Safety Is Established
We believe that it is inappropriate to grow transgenic crops in open or unsecured environments until human safety and environmental safety concerns related to both the pharmaceutical per se and the transformation can be objectively delineated and assessed. We have investigated the technical issues associated with growing agricultural crops in controlled environments and conclude that the routine production of agricultural crops in controlled environments is feasible and practical during laboratory investigation, pre-clinical and Phase I/II clinical trial stages of drug development. We believe that production in a totally controlled environment should represent the base requirement.

Mineral-depleted underground limestone mines represent the best case for production in a controlled environment. The largest single mine we have examined has 1,600 acres of mineral-depleted useable space. Several states have inventories of developable space. A single mine in a metropolitan area or serving a specific industry (steel, etc.) may create >40 acres of new space per year. Martin Marietta, the largest limestone producer in the US has operations in over 350 locations across the US. They and other companies can actually mine limestone deposits to spec's to create large-scale underground production facilities. Limestone mines are typically at depths between 50 and 200 feet below the surface, have temperatures ranging between 50 and 70 degrees F, and do not contain minerals such as Cu or Pb that represent direct health risks to workers.

Underground limestone mines offer significant advantages in environmental control for bioengineered crop production relative to the aboveground environment and regarding exposure of both workers and the public to undefined risks. Unlike greenhouses (including double envelope designs) and aboveground windowless facilities, underground mines are unaffected by wind, hail, snow or ice storms, tornados, fire, etc. Mineral-depleted limestone mines offer a secure protected biosecurity environment which lends itself to production spaces engineered on the clean corridor/dirty corridor concept widely used in animal research facilities, industrial clean rooms, etc. An underground facility can use the mass of the rock as a thermal sink for heat produced by electric lighting and avoids environmental heat gain from sunlight and the environment.

The Canadian FSIS has suggested that underground production should be considered as the norm for crop production occurring during laboratory, pre-clinical and Phase I/II clinical studies. [Plant Molecular Farming prepared by the Canadian Food Inspection Agency, Plant Health and Production Division, Plant Biosafety Office.
http://www.inspection.gc.ca/english/plaveg/pbo/mf/mf_disde.shtml]

It also appears that there may be some transgenic pharmaceuticals and similar biotech products that should not be grown in an open environment at any point because of human safety and/or environmental safety issues. For example, advanced antibiotics can be (and are being) produced in agricultural crops; and the critical question is whether widespread exposure of microorganisms in the outdoor production environment to a new medical antibiotic is appropriate? At the same time, we understand that there are significant cost-savings and drug/human safety advantages in producing pharmaceuticals and related biotech chemicals in agricultural crops. It appears to be

technically feasible and economically viable to grow many of these high-risk crops in a totally contained environment.

The ability to produce three, and potentially four, crop generations per acre per year for a crop such as corn or to move perennial biomass crops into continuous production creates new opportunities for drug/crop production. A micro-economic study on pharmaceutical production in corn published in BioPharm [Mison D, Curling J. The Industrial Production Costs of Recombinant Therapeutic Proteins Expressed in Transgenic Corn. BioPharm 13(5),48-54 (2000)] indicates that the lower threshold of cost-effectiveness is currently ~ 60 acres of corn (i.e., 200 pounds of active ingredient). With three (and potentially four) crop generations per year, total underground production would require a maximum of 20 acres of production space.

Crop Production and Monitoring Issues related to crop production are discussed in the attached manuscript. Crop monitoring issues are discussed in the manuscript with further comments provided below.

Regulatory Approach The conceptual approach defined in the Public forum in Ames presents this industry as an extension of the existing transgenic pharmaceutical industry as opposed to an extension of the existing food/feed industry. This approach is appropriate and indeed required for public acceptance. Otherwise, there will be a continuing series of gene escapes, contamination of the food/feed system, environmental problems from pharmaceuticals produced by the ag crops, unwarranted public exposures to pharmaceuticals, etc. Systems and personnel should be required to meet the same kind of standards as current industry systems and personnel.

Common Systems The amount of technical expertise and knowledge within the agricultural production sector regarding the development of GGP's/GMP's is very limited. At the same time, the opportunity for newcomers to ag production to overlook important issues and make critical mistakes in judgment that can seriously compromise the production system (safety) is enormous. At the same time, there is an acute need for regulators to look at crop production data holistically; and the existence of multiple systems (each with a different operating system and database system) creates unacceptable issues. We believe that FDA should require (or at least actively encouraged) the development of single industry-wide solutions.

Data Warehouse The environmental and site specific (soil type, irrigation, etc.) aspects of producing pharmaceuticals in agricultural crops creates unique monitoring needs verses production of transgenic drugs in fermentation or cell culture systems. For example, high winds, wet weather, plant disease and chemical injury can all lead to the establishment of molds on crops that produce toxic chemicals. If you are charged with monitoring the safety of the drug supply, you would like to be able to look at data across all production fields (irrespective of drug, manufacturer, operator, etc.). Issues that cut across drugs and fields also include production schemes, management systems, equipment used, personnel, custom applicators and more.

Site Specific Monitoring It is important that equipment used in data collection be 21CFR Part 11 compliant. This equipment is the weak link in the system with buggy systems and

non-existent QA/QC. Each device used should be equipped with a differential GPS (or better) receiver that allows the location of the device and the time of operation to be objectively defined.

Chemical and immunochemical strip tests represent a fundamental monitoring technology. Strip tests, when read by a qualified instrument provide quantitative data with high sensitivity and specificity. Properly designed and tested strip tests have "built-in" QA/QC procedures which insures data validity. The FDA should require the industry to develop a standardized reader that can be used by everyone (including consumers worried about environmental issues). Each strip should contain a bar code (or similar RfID device) which would be read by the reader at the time of use and allow traceability of that piece of data. A properly developed and configured system can produce legal quality data suitable for all regulatory uses.

Basic approaches to accomplishing this can be found in "Extraclinical IVD Markets: Growing demand from the ground up", IVD Technology, September 2001, p 35 (http://www.devicelink.com/ivdt/archive/01/09/004.html); and also "Taking IVD Test Technology Beyond Human Clinical Diagnostics", *IVD Technology*, June 2001, p. 35.

Video Surveillance The collection and subsequent analysis of real-time video surveillance data on each production field should be required. This data system provides visual confirmation of all activities which occur in a field. That is, the video surveillance data and the logs from site-specific monitoring operations should match in time and location. Video surveillance data will also identify unauthorized activities. In agriculture, there is a significant problem with misapplications of chemicals due to "simple" operator error by unaffiliated individuals. A pilot applying an ag chemical flies over the wrong field. Similar errors by ground-based applicators are common because of fatigue, fields having multiple access points, human error, etc. The most common problem is represented by a ground-based chemical applicator working in an adjacent field which applies chemical illegally (i.e., unauthorized, etc.) or inappropriately (i.e., in high winds, etc.).

Remote Imaging Aircraft based ultra-spectral remote imaging with a maximum repeat of 7 to 10 days should represent the norm for the routine monitoring on fields (both in production years and in rotation years) and of surrounding buffer strips. RI allows 100% inspection of production fields, rotation fields and buffer fields on each fly-over. In the event of a suspected gene escape, overflights can be easily extended to cover the surrounding area. Data from remote imaging will be used in many different ways (agronomic monitoring by the grower, verification of adherence to production and environmental regulations by regulatory agencies, identification of need for a specific practice and verification that it was completed, etc.) and hence is cost effective. Inspection coverage (and efficiency) is not influenced by weather (muddy fields), vegetative growth, heat/humidity for the inspectors, insects, etc. (As an alternative, multiple fiber-optic based ultra-spectral spectrometers with at least 2000 channels covering the UV, visible and near-IR bands can be attached to a high-clearance carrier and physically moved across the fields to accomplish ground-based remote imaging. This type of equipment is already being used on prototype agricultural sprayers which can identify a specific weed on the fly, and trigger a site specific spray nozzle for the appropriate chemical.)

Aircraft based RI is preferred because it minimizes cloud cover issues associated with satellites (i.e., fly below the clouds) and allows repeats to be optimized to meet crop needs. RI system needs to have high spectral resolution to objectively and accurately identify specific transformed cultivars; and the imaging bandwidth needs to span the UV to near-IR spectrum. A aircraft based system with > 1000 channels could "easily" be assembled from existing instruments for testing in 2003; and a system with 2000 channels with 1 nm bandwidth could be assembled for use in 2004 based upon existing technologies. RI system needs to have high spatial resolution, capable of identifying individual plants. Spatial resolutions of 6" and 30" seem appropriate and can be reasonably attained with aircraft based systems. The RI system needs to incorporate a real-time sun monitoring system. The RI system needs to be GPS based. RI system needs to be compliant with FDA's GGP's for this industry and 21CFR Part 11.

Because of training and use issues, the FDA should request that the pharmaceutical industry develop a common RI system which will be used across the industry. This dramatically reduces the costs of imaging and interpretation per field, makes the life of regulatory officials much simpler (one software system and a single data set for all production), etc.

The technology, including the technology for the imaging system(s) and software (database, security management needed for a common database, automated orthocorrection, image interpretation, etc.) all exist.

Grain Tracing Existing paper-based grain tracing systems don't work. A recent study by the Japanese government found that 30% of the organic tofu samples purchased in stores (and hence subject to a mandatory paper-trail based tracing system supplemented with genetic testing) were significantly contaminated with GMO soybeans.

The proposed approach of using a color identifier seems unworkable. If 400 pharmaceuticals in agricultural crops by 2011 is a reasonable estimate, that means the 3x to 5x that will have started through the system. The drugs in some of these transformations will be inherently safe (human serum albumin) while others will represent the highest level of toxicity (cancer treatment). Identifying the specific drug in a colored grain sample will be difficult, even if strip tests are available. Pharmaceuticals are being engineered into many crops other than corn where creation of a unique color is difficult. In addition, the insertion of multiple genes into a crop creates additional issues regarding gene stability, impact on crop performance, etc. Stacking traits without performance impairment is still difficult.

The best solution we have identified is a requirement to insert paper confetti into the grain stream at harvest. Confetti (paper and ink) would be GRAS. Confetti systems are inexpensive, powerful and in use today for theft prevention. It should be illegal to remove the confetti during crop handling operations (cleaning, etc.) without re-inserting the removed confetti or inserting a comparable amount of tracing confetti. An appropriate piece of confetti carries a unique number that can be decoded to identify the crop, the producer, the grain's origin (field, location within a field, time of harvest/processing, etc.), etc. A system has been designed which makes it impossible to counterfeit without detection. By storing information in a common system, tracing crops becomes very simple and provides independent verification of a paper-based (or its

equivalent electronic version) tracing system. Additional information on the counterfeit prevention system can be provided upon request.

If you need additional information, please feel free to contact me.

Sincerely,

Lon Crosby

Lon Crosby, Ph.D.
Chief Technology Officer

Attachment – BioPharm manuscript